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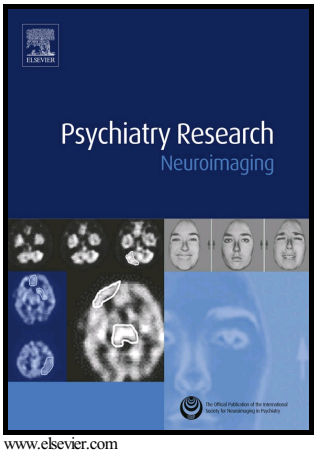

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Brain abnormalities in adults with Attention Deficit Hyperactivity Disorder revealed by voxel-based morphometry

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) commonly affects children, although the symptoms persist into adulthood in approximately 50% of cases. Structural imaging studies in children have documented both cortical and subcortical changes in the brain. However, there have been only a few studies in adults and the results are inconclusive. **Method:** Voxel-based morphometry (VBM) was applied to 44 adults with ADHD, Combined subtype, aged 18-54 years and 44 healthy controls matched for age, sex and IQ. **Results:** ADHD patients showed reduced grey matter (GM) volume in the right supplementary motor area (SMA). Using more lenient thresholds we also observed reductions in the subgenual anterior cingulate (ACC) and right dorsolateral prefrontal (DLPFC) cortices and increases in the basal ganglia, specifically in the left caudate nucleus and putamen. There was a positive correlation between the cumulative stimulant dose and volume in the right SMA and DLPFC clusters. **Conclusions:** The findings suggest that adults with ADHD show brain structural changes in regions belonging to the so-called cool executive function network. Long-term stimulant medication may act to normalize these GM alterations.

Key words: ADHD, Neuroimaging, Voxel-Based Morphometry, Methylphenidate, supplementary motor area, anterior cingulate cortex, dorsolateral prefrontal cortex.

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent neuropsychiatric disorders, affecting about 5% of children (Polanczyk et al., 2007). Although it was originally believed to be a disorder of childhood, there is evidence that the symptoms persist into adulthood in approximately 50% of cases (Pironti et al., 2014). In adults, symptoms of hyperactivity, impulsivity and deficit of attention tend to be expressed in the form of inner restlessness, inability to relax, impatience, difficulty to make decisions, affective instability and stress intolerance (Kooij et al., 2010). These symptoms can significantly disrupt patients' daily life activities, especially in the absence of adequate coping skills (Amico et al., 2011).

Numerous structural neuroimaging studies have examined ADHD in children. A meta-analysis of studies using region of interest (ROI) analyses found reductions in overall brain volume, and in several frontal regions, the posterior inferior cerebellar vermis, the splenium of the corpus callosum and the right caudate nucleus (Valera et al., 2007) ROI analysis however, has the disadvantage that examined areas are selected a priori meaning that changes in non-selected areas or in areas that do not conform to known anatomical divisions may be missed (Rubia et al., 2014). Whole brain techniques like voxel-based morphometry (VBM) avoid this problem, comparing all cortical and subcortical grey matter (GM) between patients and controls at once and automatically generating clusters where changes are maximal (Hoekzema et al., 2012). Studies applying VBM to children with ADHD have broadly confirmed the findings of ROI studies but have documented a more detailed pattern of volume

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reductions in the frontal lobe, including the dorsolateral and orbitofrontal cortices, as well as finding volume reductions in subregions of the temporal, parietal and occipital lobes and the anterior and posterior cingulate cortex (Cubillo et al., 2012; De La Fuente et al., 2013; Hoekzema et al., 2012). Different meta-analysis of these studies found reductions in GM, especially in the basal ganglia, as well as slightly greater GM volumes in the left posterior cingulate cortex (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011). However, the meta-analysis of Nakao et al. (2011) also found evidence for normalization of the basal ganglia changes with age and in association with the use of stimulant medication.

Whereas structural imaging studies of children with ADHD are plentiful, there have been only a few studies in adults with the disorder. These studies have mostly focused on evaluating if patients share GM abnormalities in fronto-striato-cerebellar circuits that sustain attention, inhibition, cognitive control, motivation, and emotion but the results are inconclusive. Studies using a whole-brain analysis did not detect significant differences between patients and controls(Amico et al., 2011; Onnink et al., 2014; Pironti et al., 2014; Seidman et al., 2011; Seidman et al., 2006), except for the studies of Ahrendts et al. (2011) and Almeida et al. (2010). The former found that ADHD patients showed a significant reduction in GM volume bilaterally in the occipital lobes (Ahrendts et al., 2011), and the latter showed reductions in the right caudate nucleus (Almeida Montes et al., 2010). However, some of these studies in adult population carried out an exploratory ROI analysis and found that compared to healthy subjects, ADHD patients showed deficits in overall cortical GM (Seidman et al., 2006), various regions within the frontal lobe, including the orbitofrontal and

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dorsolateral cortices and the inferior frontal gyrus, the anterior cingulate cortex, the parietal and occipital lobes, the cerebellum and the caudate and putamen nuclei (Almeida Montes et al., 2010; Amico et al., 2011; Hesslinger et al., 2002; Onnink et al., 2014; Pironti et al., 2014; Seidman et al., 2011; Seidman et al., 2006). Also, one study reported an increase of GM volume in regions within the occipital and parietal lobes, the dorsolateral prefrontal cortex and the dorsal mid cingulate cortex in ADHD patients relative to controls (Pironti et al., 2014).

The discrepancies between childhood and adult brain structural findings in ADHD could be genuine, perhaps reflecting the above mentioned meta-analytic finding that increasing age and treatment with stimulants may tend to normalize brain structure (Nakao et al., 2011). Alternatively, they could simply be a function of the relative lack of studies in ADHD adult population, their generally smaller sample sizes, or possibly other factors related to the inclusion of comorbid conditions or no discrimination between ADHD subtypes (Cortese and Castellanos, 2012; Spencer et al., 2013).

In the present study, we evaluated changes in a larger sample of adults with ADHD and controls using a VBM analysis. We also investigated the association between changes found and clinical factors and exposure to stimulant medication.

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2. Methods

2.1. Participants

Forty-six right-handed adult ADHD combined subtype (ADHD-C) were recruited from the Hospital Universitari Vall d'Hebron and the Benito Menni CASM. Two ADHD patients were excluded from the analyses due to movement in the MRI images, therefore, our final sample consisted of forty-four patients (demographic data for the sample is shown in **Table 1**).

Clinical diagnosis was made by a team of ADHD expert psychiatrists and psychologists, based on the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Test Revised (DSM-IV-TR) (APA., 2004) and confirmed with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein and Johnson, 1999; Ramos-Quiroga et al., 2012), the Wender Utah Rating Scale (WURS) (Ward et al., 1993), the ADHD Rating Scale (DuPaul, 1998) and the Conners Adult ADHD Rating Scale (CAARS) (Conners, 1999). Exclusion criteria were (a) age younger than 18 or older than 65 years, (b) left-handedness, (c) history of brain trauma or neurological disease, and (d) substance use disorder (abuse/dependence) of drugs including cocaine, heroin, synthetic drugs or alcohol. All subjects were evaluated to exclude comorbidity with other major psychiatric or personality disorders using the Structured Clinical Interview for Axis I (SCID-I) (First et al., 2002) and Axis II (SCID-II) (First et al., 1997) respectively to prevent that the findings of our study

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reflected brain abnormalities not related to ADHD per se but to its comorbid disorders.

Twenty-nine patients were medicated only with methylphenidate (mean ± SD; relative daily doses (mg/day) 42.24 ± 16.17; treatment duration (months) 25.20 ± 24.41) and 15 had never received any pharmacological treatment. The stimulant-treated ADHD patients were discontinued at least 4 days prior to the MRI.

The control sample consisted of forty-four right-handed healthy individuals recruited from non-medical staff working in the hospital Benito Menni CASM, their relatives and acquaintances, plus independent sources in the community. They met the same exclusion criteria as the ADHD group. Although they were not assessed using specific clinical scales of ADHD, they were interviewed by a group of clinical psychologists and were excluded if they had any psychiatric disorder or were taking any type of psychotropic medication other than non-regular use of benzodiazepines or other similar drugs for insomnia. They were also questioned about family history of mental illness and excluded if a first-degree relative had experienced symptoms consistent with major psychiatric disorder and/or if they had received in- or outpatient psychiatric care.

Both the ADHD and control group were matched for age, gender and IQ, as estimated by the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Del Ser et al., 1997), a test requiring pronunciation of Spanish words whose accents have been removed. The TAP has been standardized against the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 2001) and scores can be converted into full-

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scale IQ estimates (Gomar et al., 2011). Both groups were also required to have a current IQ in the normal rang (>70 points), as measured using two subtests of the WAIS-III: vocabulary and block design.

The study was approved by the Ethics Committee of both hospitals and all participants gave written informed consent.

2.2. Brain data acquisition

All participants were scanned in the same 1.5-T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI, USA) at Sant Joan de Déu Hospital in Barcelona (Spain) using the following high-resolution structural T1 MRI sequence: 180 axial slices, 1mm slice thickness with no gap, 512×512 matrix size, 0.5×0.5×1mm3 voxel resolution, 4ms echo time, 2000ms repetition time, 15° flip angle.

2.3. Image processing

Raw structural images had the non-brain matter removed with the 'brain extraction tool' (BET) (Smith 2002) and were segmented into GM and other tissues with the FMRIB software library (FSL) (Zhang et al., 2001).

Normalization of the GM segments to a common template was conducted with the 'advanced normalization tools' (ANTS) high-resolution diffeomorphic symmetric

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normalization (SyN) based on directly manipulated free form deformation (Avants et al., 2008; Avants et al., 2010), which has shown to substantially improve the accuracy of other methods (Klein et al., 2009). Normalization steps were as follows: a) affine registration of the native-space GM images to a MNI GM template (voxel-size: 1.5x1.5x1.5mm3); b) creation of a template by the registered GM images; c) non-linear registration of the native-space GM images to the template; and d) four extra iterations of the steps b and c. Modulated and non-modulated images were Gaussian-smoothed with a σ=4mm (FWHM=9.4mm) kernel, which has shown to yield increased sensitivity as compared to narrower kernels (Radua et al., 2014).

It has been shown that that the non-linear registration is able to capture gross differences such as brain shape abnormalities, but not more subtle differences such as fine cortical thinning (Radua et al., 2014). Thus, unmodulated images may better detect mesoscopic (i.e. between microscopic and macroscopic) differences not captured by the non-linear registration, as in that case the modulation would only introduce macroscopic noise, ultimately reducing the statistical power (Radua et al., 2014). Conversely, modulated images may better detect macroscopic differences captured by the non-linear registration, as a great part of these differences might be removed during the non-linear registration but re-introduced with the modulation (Ashburner and Friston, 2001).

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213 **2.4. Statistical analysis**

214

215 Demographic and clinical data. Differences in demographic and clinical
216 characteristics among the groups were examined using chi-square tests for
217 categorical variables and independent sample t-tests for continuous variables.

218

219 Inter-group VBM comparisons. Voxel-based anatomical differences between patients
220 and controls were fitted with a general linear model. Sex, age and cumulative
221 stimulant dose were included as regressors in order to reduce the error of the model;
222 please note that these variables have known relations with GM volume, and that the
223 previous matching by sex and age was useful to remove the potential confounding
224 effect of these variables but not to reduce the within-group variability associated to
225 them. We used the 'threshold-free cluster enhancement' (TFCE) due to its increased
226 sensitivity as compared to voxel- or cluster-based statistics (Radua et al., 2014;
227 Salimi-Khorshidi et al., 2011; Smith and Nichols, 2009). Statistical significance was
228 assessed with the permutation test included in FSL and maps were threholded twice,
229 once using a family-wise error (FWE) corrected $p < 0.05$ and once using an
230 uncorrected $p<0.001$ (in both cases conventionally excluding clusters with less than
231 10 voxels). This was on the basis that the former will tend to minimize false positive
232 results whilst the latter will minimize false negative results (Durnez et al., 2014).

233

234 Correlation analysis. GM volume within clusters of statistically significant difference
235 between patients and controls was extracted (by) for further analysis within the
236 patient sample. Specifically, we first computed, for each patient, the mean of the

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voxels included in each cluster and then calculated the Pearson correlation coefficient between these individual means and the cumulative stimulant dose, the ADHD Rating Scale scores and the inattention, hyperactivity, impulsivity and ADHD total subscales of the CAARS in order to explore whether these factors might have an influence on ADHD GM abnormalities.

3. Results

3.1. Participants

Demographic and clinical data for the ADHD and control groups are shown in **Table 1**. Both groups were well-matched for age, gender and estimated premorbid IQ (TAP score). Both groups did not differ significantly in educational level.

[Table 1 about here]

3.2. Modulated VBM analysis

Compared to the healthy subjects, ADHD individuals showed three clusters of GM reduction. One was situated in the right supplementary motor area (SMA) extending to superior frontal lobe (cluster size: 889 voxels; uncorrected $p<0.001$, FWE-corrected $p<0.05$; MNI x=8 y=24 z=64), another cluster was located in the subgenual anterior cingulate cortex (ACC) (cluster size: 53 voxels; uncorrected $p<0.001$; MNI x=6 y=18 z=-14) and a third was in the right dorsolateral prefrontal cortex (DLPFC)

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(cluster size: 16 voxels; uncorrected $p<0.001$; MNI x=48 y=18 z=44). There were no cortical or subcortical regions where ADHD patients showed more GM volume than controls (see **Table 2** and **Figure 1**). Findings in ACC and DLPFC did not survive the correction for multiple comparisons.

[Table 2 and Figure 1 and 2 about here]

3.3. Unmodulated VBM analysis

ADHD patients did not show any brain regions with less GM relative to the control group. However, they showed a cluster of GM increase relative to the controls situated in the basal ganglia, specifically in the left caudate nucleus and putamen (cluster size: 15 voxels; uncorrected $p=0.001$; MNI x=-8 y=12 z=-2) (see **Table 2** and **Figure 1**). This finding did not survive the correction for multiple comparisons.

3.4. Correlational analysis

There was a significant positive correlation between the cumulative stimulant dose and the clusters of GM reduction in the right SMA (extending to the superior frontal cortex) and in the right DLPFC (see **Table 2 and Figure 2**). Specifically, higher cumulative dose was associated with larger (i.e. less abnormal) volume of these areas. There were no statistical significant correlations with clinical measures.

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4. Discussion

The aim of this study was to evaluate whether there are volumetric differences between adults with ADHD and healthy subjects. A modulated VBM analysis showed a macroscopic reduction of GM volume in the right SMA, the subgenual ACC and the right DLPFC. Using the unmodulated approach we found a mesoscopic increase of GM density in the left caudate and putamen nuclei. Only the abnormality in SMA survived the correction for multiple comparisons, and no statistically significant alterations were detected in brain regions reported in other studies such as the orbitofrontal cortex, the occipital and parietal lobes and the cerebellum (Ahrendts et al., 2011; Hesslinger et al., 2002; Pironti et al., 2014; Seidman et al., 2011; Seidman et al., 2006).

This is the first volumetric study in ADHD adult population that has shown smaller GM in the SMA. Functional neuroimaging studies suggest that a network of fronto-parietal brain regions -including the inferior prefrontal, medial prefrontal (the SMA and pre-SMA) and inferior parietal areas, are implicated in motor response inhibition (Hart et al., 2013), with SMA as one of the key motor inhibition areas (Hart et al., 2014). This may be significant, since some psychological theories have proposed that ADHD symptoms result from a primary deficit in inhibitory control (Barkley, 1997). In this respect it is also interesting to note that a study carried out in pediatric ADHD patients found that the left supplementary motor complex (SMC) emerged as the most anomalous frontal lobe region in these patients (Mahone et al., 2011).

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Despite reductions in ACC and DLPFC were only significant using lenient thresholds, they support the findings of Amico et al. (2011) and Seidman et al. (2006, 2011) showing a smaller volume in ACC and the DLPFC in adult patients with ADHD. According to previous literature in childhood, our findings are also consistent with respect to significant reductions in these structures (De La Fuente et al., 2013). On the one hand, the role of the ACC is far beyond the processing and regulation of emotional information, i.e. the projections from the ACC to the motor cortex and spinal cord seem to implicate this region in motor control (Frodl and Skokauskas, 2012). In fact, a meta-analysis published by Hart et al. (2013) in functional MRI, reports that both the SMA and the ACC showed a decreased activation in patients with ADHD compared with healthy controls during performance of different inhibition tasks (Hart et al., 2013). Relative to the DLPFC it is an important region involved in the executive functions which are highly affected in ADHD patients. In fact, anatomical studies in children have shown volume reductions in this structure relative to controls and functional studies have shown underactivation of the DLPFC during different cognitive and motor tasks. Therefore, many investigators hypothesize DLPFC dysfunction in the etiology of the disorder (Cubillo et al., 2012; Seidman et al., 2006).

Our data do not replicate the results of Seidman et al. (2011) and Almeida et al. (2010) of significantly less volume in putamen and caudate nuclei in adult patients with ADHD. On the contrary, our results showed a cluster of GM increase relative to the healthy comparison group in the basal ganglia (left caudate and putamen nuclei), supporting a positive association in ADHD patients between age and GM increase in

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these regions. Caudate and putamen integrate the fronto-striato-thalamo-cortical circuit, mediating cognitive executive functions and motor activity, typically impaired in ADHD. Volumetric reductions in basal ganglia typically reported in childhood ADHD, would not only seem to diminish over time from childhood to adulthood, but the size of these structures in adult ADHD could actually increase in relation to healthy controls, as a compensatory striatal overgrowth of frontal deficits to prevent cognitive and motor behavioral inhibitory output impairment. These data support the results found in the last meta-analyses by Nakao et al. (2011) and Frodl and Skokauskas (2012), reporting a positive association between age and GM increase in the basal ganglia in ADHD patients. However, our findings in basal ganglia were not significant after correction for multiple comparisons and should thus be taken with caution.

The correlation analysis showed no correlation between clinical measures and the volumetric abnormalities. However, there was a significant correlation between cumulative stimulant dose and the volume of the right SMA and the right DLPFC; this was positive in both cases, i.e. a greater exposure to stimulant treatment was associated with less volume reduction. Previous studies using the ROI approach found that pediatric patients who had been medicated with psychostimulants did not show volume reductions in regions like the ACC, the pulvinar nucleus of the thalamus, the posterior inferior cerebellum and the corpus callosum compared with typically developing children (Bledsoe et al., 2009; Ivanov et al., 2014; Semrud-Clikeman et al., 2006), suggesting a neuroprotective effect of stimulants on brain development in the disorder (Rubia et al., 2013). A further study using cortical

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thickness analysis also found evidence that unmedicated children with ADHD showed excessive cortical thinning compared with control subjects, whereas children treated with psychostimulants did not (Shaw et al., 2009). Finally, a recent meta-analysis of VBM studies found that long-term stimulant medication was associated with more normal basal ganglia structure (Nakao et al., 2011). The effects of stimulant treatment on brain function in ADHD patients has received more attention, with reports that methylphenidate induces acute normalization of activation patterns in different networks of the brain such as the fronto-striatal and the fronto-cingulate that include brain regions that have been associated with structural and functional changes in ADHD (Rubia et al., 2011a; Rubia et al., 2011b).

This study has some limitations. First, results other than those in SMA did not survive after correction for multiple comparisons and should be thus taken with caution. Second, neuropsychological assessment was not sufficient in order to conduct an analysis of correlation between the brain changes found and neuropsychological measures, therefore we could not assess whether there was an association between these variables. Finally, it is important to remember that the cases with comorbid substance abuse and other major psychiatric disorders in Axis I and II were excluded from the study, so there is a limitation to generalize the result of the study to ADHD subjects with other substance use or psychiatric disorders. However, the use of a clinical sample with no comorbidities, whilst a possible limitation for generalizing our results provided that comorbidity is very prevalent in adult ADHD (Asherson et al., 2007; Kessler et al., 2006), is the only way to enable a better characterization of ADHD per se in order to attribute neuroimaging findings to the disorder itself.

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In summary, our results in a large sample of ADHD adults using a whole brain VBM analysis show that patients with ADHD have a GM volume reduction in the right SMA, the subgenual ACC and the right DLPFC and an increase of GM density in the left caudate and putamen relative to controls. All these regions mediate cognitive and motoric functions such as motor response and interference inhibition, cognitive flexibility, temporal foresight, selective and sustained attention, working memory, motor and timing processes which are dysfunctional in ADHD patients (Castellanos et al., 2006; Cubillo et al., 2012). Findings of GM reduction circumscribed to frontal regions only, with no significant findings for cerebellar, occipital, temporal nor parietal regions in our adult ADHD sample, give support to the hypothesis of developmental structural brain differences in ADHD normalizing with increasing age (Onnink et al., 2014; Shaw et al., 2007), with maintenance of volume reduction only with respect to frontal lobe during adulthood.

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Conflict of interest: The authors declare that they have no conflict of interest.

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LEGENDS

Table 1

TAP, Word Accentuation Test (Test de Acentuación de Palabras); TAP_FISQ, TAP-estimated Full-scale IQ; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; WURS, Wender Utah Rating Scale; ADHD, Attention Deficit Hyperactivity Disorder; CAARS, Conners Adult ADHD Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Diseases.

Table 2

Analyses covaried by age, sex and cumulated stimulant dose. (a) $p < 0.001$ uncorrected for multiple comparisons, 10 voxels extent threshold. (b) This result was also significant ($p < 0.05$) after correction for multiple comparisons. ADHD Attention Deficit Hyperactivity Disorder, SMA supplementary motor area, ACC anterior cingulated cortex, DLPFC dorsolateral prefrontal cortex. r, Pearson correlation coefficient; n.s, no significant.

Figure 1

Volumetric differences in patients with ADHD relative to healthy subjects. Areas in blue indicate a significant less gray matter in patients relative to control group; areas in red indicate a significant more gray matter density in ADHD compared to controls. Reductions in ACC and DLPFC and increase in basal ganglia were not significant after correction for multiple comparisons.

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Figure 2

Boxplots and scatterplots of the relationships between gray matter, group (healthy controls, drug-naïve patients and medicated patients) and cumulated medication dose.

Table 1. Demographic and clinical characteristics of the sample

	ADHD N=44 Mean (SD)	Control N=44 Mean (SD)	P value	χ^2 value
Age (years)	31.61 (11.38)	32.57 (10.63)	0.68	
Sex (male/female)	29/15	29/15		1.00
Education (years)	17.96 (3.76)	18.38 (4.53)	0.70	
TAP, mean	22.42 (4.49)	23.10 (3.88)	0.47	
TAP_FISQ	101.24 (8.06)	102.38 (7.45)	0.53	
Current IQ (WAIS-III)	105.00 (7.53)	105.97 (11.38)	0.66	
WURS	51.95 (11.09)			
ADHD Rating Scale	32.15 (9.12)			
CAARS				
Inattention	22.29 (7.68)			
Hyperactivity	20.80 (8.45)			
Impulsivity	18.56 (7.84)			
Problems with self-concept	9.51 (4.34)			
DSM-IV inattentive symptoms	17.49 (4.88)			
DSM-IV hyperactivity-impulsivity symptoms	15.80 (6.64)			
DSM-IV total ADHD symptoms	33.29 (9.85)			
ADHD Index	21.61 (6.08)			

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Table 2. Gray matter volumetric differences between patients with ADHD and healthy controls.

	Peak		Cluster size	Association with cumulative stimulant dose
	MNI	P (a)		
Macroscopic changes (modulated data)				
Increases of volume (ADHD > Controls)				
(none)				
Decreases of volume (ADHD < Controls)				
Right SMA, extending to superior frontal	8,24,64	<0.001 (b)	889	r = 0.451 (p = 0.002)
Subgenual ACC	6,18,-14	<0.001	53	n.s.
Right dorsolateral prefrontal cortex	48,18,44	<0.001	16	r = 0.407 (p = 0.006)
Mesoscopic changes (unmodulated data)				
Increases of volume (ADHD > Controls)				
Left caudate and putamen	-8,12,-2	0.001	15	n.s.
Decreases of volume (ADHD < Controls)				
(none)				

(a) $p < 0.001$ uncorrected for multiple comparisons, 10 voxels extent threshold.

(b) This result was also significant ($p < 0.05$) after FWE-correction for multiple comparisons.

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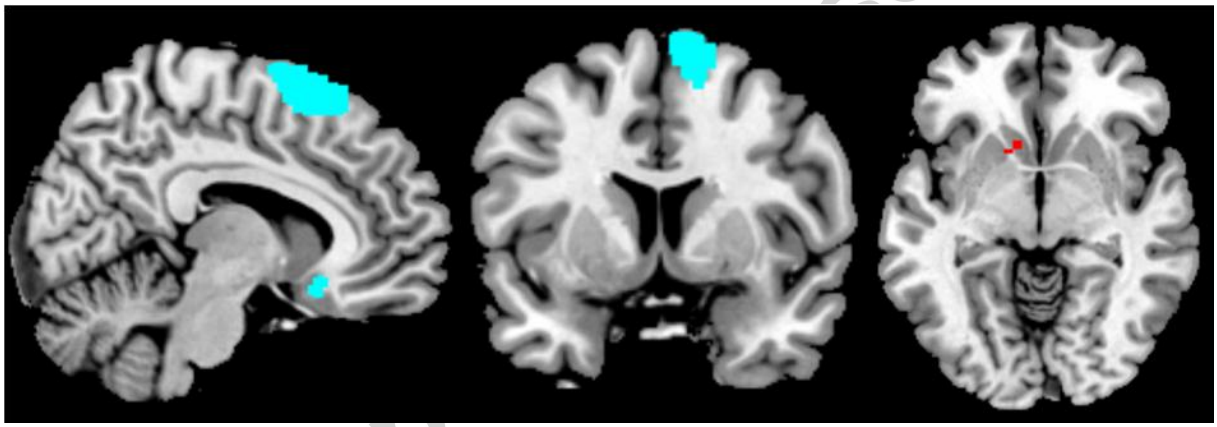
Highlights

- Anatomical MRI images are obtained using voxel-based morphometry (VBM) from a large sample of adults with ADHD-Combined subtype and a matched group of healthy volunteers

- ADHD adults show structural abnormalities in key regions of cognitive control

- Long-term stimulant medication may act to normalize brain structural deficits in patients with ADHD



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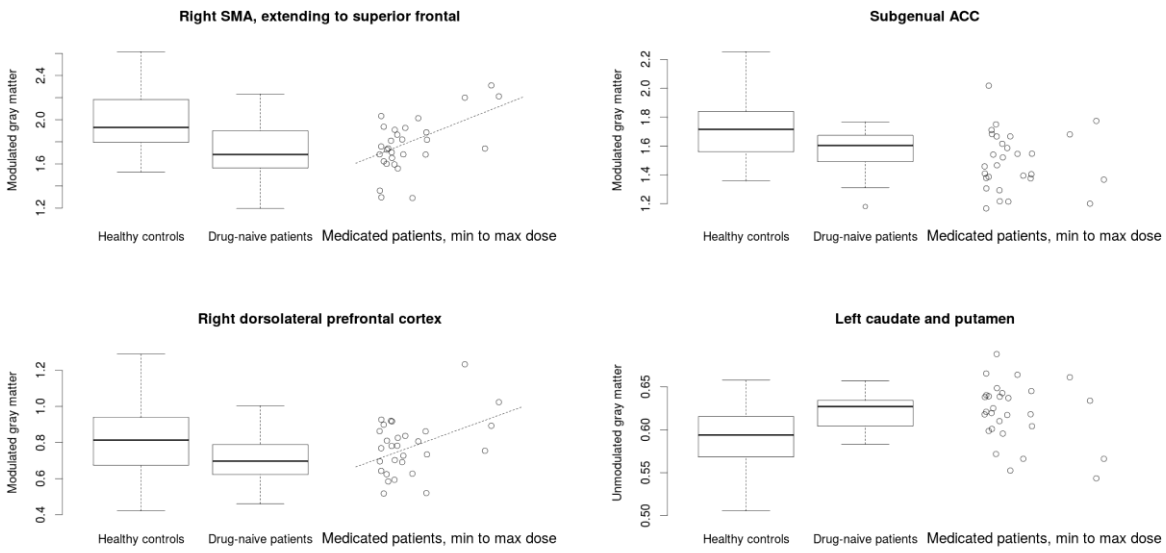

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